⑤ · Ulcerative colitis

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Infliximab in severe steroid-refractory ulcerative colitis: A pilot study

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Infliximab bei schwerer steroidrefraktärer Colitis ulcerosa: Eine Pilot-Studie

Zusammenfassung. Neutralisation von Tumor Nekrose Faktor α (TNFα) durch Infliximab ist effektiv in der Behandlung des chronisch-aktiven Mb. Crohn (CD). Wir testeten eine einmalige Infusion von 5 mg/kg Infliximab im Rahmen einer open-label Pilot-Studie bei sechs Patienten mit schwerer, steroid-refraktärer Colitis ulcerosa (UC). Die klinische Aktivität wurde nach Lichtiger an den Tagen –1, 7 und 28 bewertet. Kolonoskopien mit Biopsien wurden am Tag –1 und 7 durchgeführt. Alle Patienten zeigten eine deutliche klinische Besserung am Tag 7 (nach Lichtiger: 16,3 ± 0,4 [Tag –1] vs 4,8 ± 0,7 [Tag 7], $P < 0{,}0001$). Vier der sechs Patienten zeigten eine Langzeit-Remission (nach Lichtiger: 7,7 ± 2,2 [Tag 28], $P < 0{,}01$ verglichen mit Tag –1) bei einer medianen Nachbeobachtungszeit von 5,5 Monaten. Die Kolonoskopien bestätigten die signifikante Besserung der endoskopischen Läsionen. Das inflammatorische Infiltrat verschwand auf H&E-Färbungen, verbunden mit einer deutlichen Reduktion an infiltrierenden Neutrophilen. Die semiquantitative immunhistochemische Auswertung von T- und B-Lymphozyten und Makrophagen zeigte keine wesenlichen Unterschiede verglichen zur Ausgangssituation, während apoptotische Zellen in der Mucosa am Tag 7 reduziert waren. Unsere Daten deuten auf eine neue Behandlungsoption bei schwerer aktiver steroid-refraktärer UC hin und verlangen nach entsprechenden kontrollierten Studien.

Schlüsselwörter: Colitis ulcerosa, TNFα, entzündliche Darmerkrankung, Infliximab.

Summary. Tumor necrosis factor-α (TNFα)-neutralization by infliximab has previously proven efficacious in chronic active Crohn's disease (CD). We performed an open-label pilot study of a single infusion of 5 mg/kg infliximab in six patients with severe active, steroid-refractory ulcerative colitis (UC). Clinical activity was evaluated according to Lichtiger on days –1, day 7, and day 28. Colonoscopy with biopsy was performed on day –1 and day 7. All patients showed marked clinical improvement by day 7 (Lichtiger score 16.3 ± 0.4 [day –1] vs 4.8 ± 0.7 [day 7], $P < 0.0001$). Four of six patients had long-term remission (Lichtiger score 7.7 ± 2.2 [day 28], $P < 0.01$ compared to day –1), with a median follow-up of 5.5 months. Colonoscopy confirmed significant healing of endoscopic lesions. The inflammatory infiltrate disappeared on H&E stains, with a marked reduction in infiltrating neutrophils. Semiquantitative evaluation of T and B lymphocytes and macrophages by immunohistochemistry did not reveal major differences compared to pre-treatment. Apoptotic cells in the mucosa were reduced on day 7. Our data point toward a novel efficacious treatment option in severe steroid-refractory UC and raise the need for controlled trials.

Key words: Ulcerative colitis, TNFα, inflammatory bowel disease, infliximab.

Introduction

UC and CD are two manifestations of inflammatory bowel disease (IBD), with a prevalence of 150–200 cases per 100.000 in the western world, whose etiologies are unknown [1]. UC is confined to the large bowel and is characterized by superficial inflammation of the mucosa. In contrast, CD presents as transmural inflammation and may affect all parts of the gastrointestinal tract [2]. Several lines of evidence support the concept that the pathogenesis of CD is related to overexpression of Th1 cytokines (Interferon-γ, TNFα) in the gut wall, while UC is linked to a dysregulated Th2 response (e.g. Interleukin-5) [3]. However, increased expression of TNFα has been reported in involved colon in UC [4].

Infliximab (formerly known as cA2; Centocor, Malvern, PA) is a chimeric immunoglobulin (Ig) G1κ murine-human monoclonal antibody developed as a therapeutic agent for TNFα-mediated diseases [5]. Infliximab has been shown to neutralize TNFα effects by blocking soluble TNFα and binding to transmembrane TNFα. Randomized, controlled trials have shown significant clinical and endoscopic benefits of infliximab treatment in active refractory CD [6, 7].

Therapeutic options in steroid-refractory UC are limited. Current clinical practice includes the administration of cyclosporine and azathioprin, and eventually patients have to undergo debilitating surgical resections.

Subjects and methods

We performed an open-label pilot study of infliximab in six patients with severe active UC despite high doses of intravenous steroids. Two male and four female patients (age range:

22–76) with a disease duration ranging from 2 months to 11 years presented with pancolitis. The criteria of Lockhart-Mummery and Morson were used to establish the diagnosis of ulcerative colitis and to distinguish this form of colitis from Crohn's colitis [2]. UC clinical activity was assessed according to Lichtiger et al. [8]. Patients were eligible to enter the study if they had no response to intravenous corticosteroid therapy (equivalent to a daily dose of 1.5 mg/kg prednisolone) after seven or more days [8]. After they had given informed consent, the patients received a single infusion of 5 mg/kg infliximab as a two-hour infusion. In five patients colonoscopy with biopsies was performed before treatment and on day +7. In addition to H&E stains, immunohistochemistry was performed with antibodies directed against CD3, CD4, CD8, CD20, and CD68. Neutrophils were identified by staining for naphthol AS-D chloroacetate-esterase (NASD). Apoptosis was assessed by terminal deoxynucleotidyl transferase-mediated dUTP-FITC nick end labeling (TUNEL). Positive staining cells were semiquantitatively assessed in a blinded fashion by an expert gastrointestinal pathologist (T.M.).

Results

Patient characteristics are displayed in Table 1. A single infusion of infliximab resulted in dramatic clinical improvement in all patients within 1–2 days after administration, causing a significant drop in clinical-activity score as assessed on day 7 compared to pre-treatment (16,3 ± 0,4 [day −1] vs 4,8 ± 0,7 [day 7] $P < 0.0001$, paired Student's t-test). Although two of six patients relapsed by week 4, the average clinical-activity score remained markedly improved compared to pre-treatment (7.7 ± 2.2, [day 28] $P < 0.01$). The other four patients remained in clinical remission during the entire follow-up period (median 5.5 months). Early colonoscopy performed seven days after administration of infliximab showed profound endoscopic improvement of inflammation compared to pre-treatment. Representative endoscopic images are shown in Fig. 1. H&E stains of colonic biopsies demonstrated corresponding reductions of inflammatory infiltrates with disappearance of crypt abscesses and restoration of mucosal architecture (Fig. 1). The cellular composition of the inflammatory infiltrate was assessed semiquantitatively by immunohistochemistry and NASD-staining. No significant quantitative changes in T lymphocytes (CD3) and subsets (CD4, CD8), B lymphocytes (CD20), and macrophages (CD68) were noted (data not shown). However, a marked decrease in neutrophils (NASD) was observed (Fig. 1), which seemed to correlate directly with clinical improvement. The number of apoptotic cells identified by TUNEL was reduced in the lamina propria upon infliximab treatment (Fig. 1).

Discussion

Six patients with severe UC refractory to high doses of steroids were enrolled in our open-label study. The clinical improvement in all patients within hours after administration of infliximab was impressive. Since four of six patients experienced long-term remission, treatment with infliximab might result in a profound change in the course of the disease and points toward a central role of TNFα in UC. Thus, the pattern of clinical response to infliximab might be comparable in CD and UC. As recently reported, in chronic-active CD almost 90% of patients initially responded to a single infusion of infliximab, with subsequent varying durations of clinical remission [9].

Regarding the cellular infiltrate, the most prominent feature was the decrease in neutrophil infiltration in the lamina propria. A complete disappearance of neutrophils and a marked reduction in mononuclear cells has been reported in chronic-active CD four weeks post infliximab [7]. In our study, in UC no remarkable alterations in T and B lymphocyte and macrophage counts were noted. This might be related to the early time-point chosen for re-evaluation after treatment, and a reduction in infiltrating mononuclear cells as described in CD might be a more de-

Table 1

Patient	Sex	Age	UC treatment pre infliximab	Clinical-activity score			Follow-up	UC treatment post infliximab
				d-1	d7	d28		
1	m	49	Prednisolone, metronidazole	15	4	4	7 months	Salazopyrin
2	w	34	Prednisolone	17	4	15	7 months relapse after 1 month	Cyclosporine, azathioprine
3	w	76	Prednisolone, salazopyrin, metronidazole, ciprofloxacin	17	5	5	6 months	Salazopyrin
4	m	49	Prednisolone, salazopyrin, metronidazole, ciprofloxacin	15	5	5	5 months	Azathioprine
5	w	48	Prednisolone, salazopyrin, metronidazole	17	8	14	5 months relapse after 1 month	Cyclosporine, azathioprine
6	w	22	Prednisolone, salazopyrin, azathioprine for 3 months	17	3	3	4 months	Azathioprine

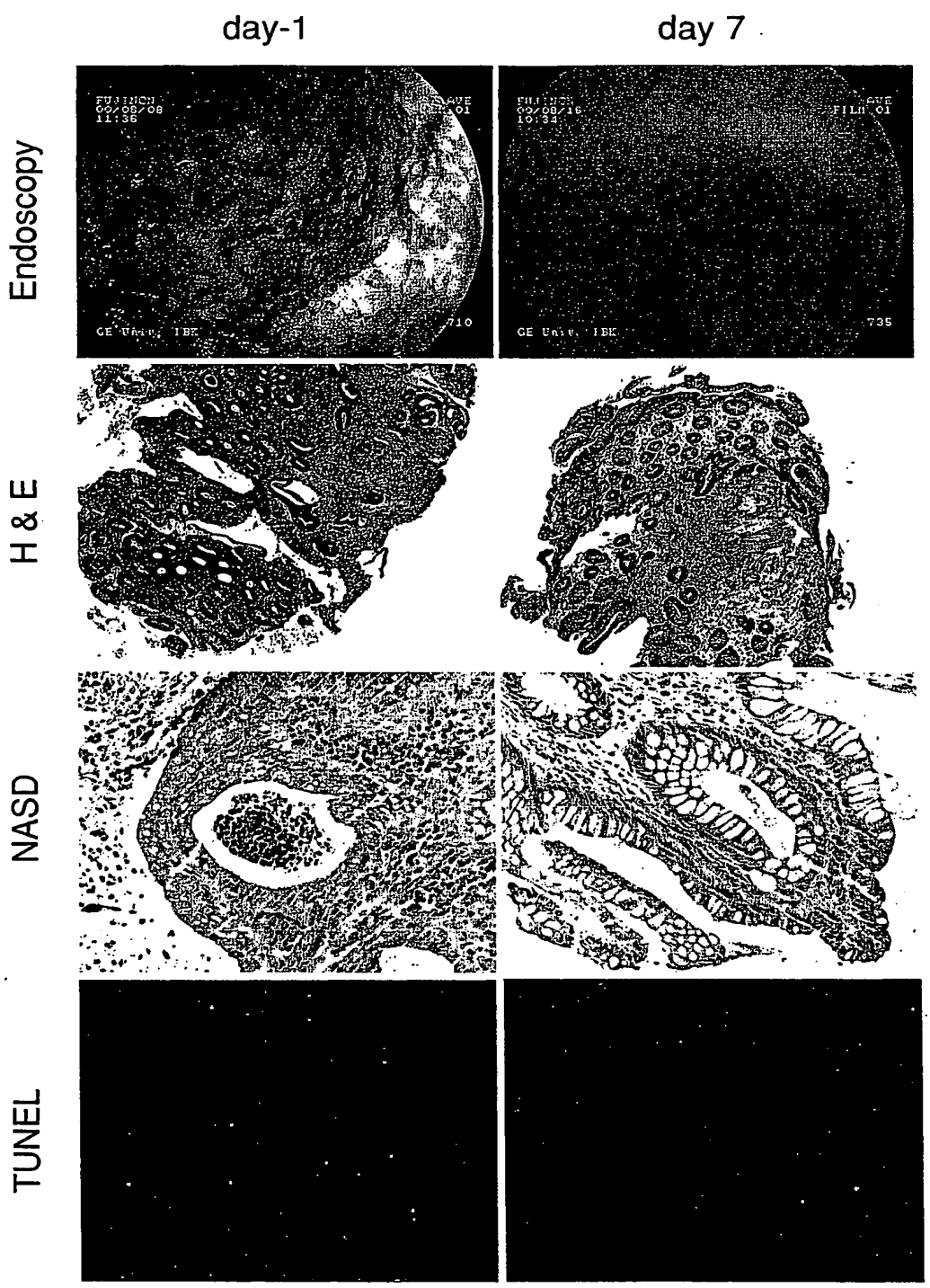

Fig. 1. Colonoscopy was performed pre-treatment (*"day -1"*) and seven days (*"day 7"*) after administration of 5 mg/kg infliximab. Representative corresponding endoscopic pictures, H&E-stains (40×), stainings of neutrophils by naphthol AS-D chloroacetate-esterase (NASD; 200×; dark red: neutrophils, orange: erythrocytes), and identification of apoptotic cells by TUNEL (200×) are presented

layed effect of infliximab treatment in UC. Furthermore, our data indicate that enhanced apoptosis of inflammatory cells, especially mononuclear cells, might not have a prominent role seven days post treatment. The decrease of apoptotic cells in the gut wall upon infliximab treatment might simply be related to the decrease in the absolute numbers of short-lived neutrophils.

Especially the potential long-term response of TNFα neutralization by infliximab challenges the view of UC as a Th2-mediated disease [3]. In contrast, a solely short-lived response toward infliximab could be argued in the Th2 concept as a blockade of a common final inflammatory pathway, leading to abrogation of acute inflammatory effects.

The data reported herein from a pilot study of infliximab in severe, active steroid-refractory UC might point toward a novel efficacious treatment option, and thus raises the need for a large, controlled trial. While this manuscript was under preparation, Sands et al. and Chey et al. reported comparable data on the efficacy of infliximab in severe, active steroid-refractory UC patients [10-12]. Two scenarios for the use of infliximab in UC might be anticipated: First, as an alternative regimen for cyclosporine, with the potential advantage of fewer side effects, and second, as a bridging therapy until the onset of action of azathioprine.

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